REMARKS/ARGUMENTS

Claims 31 and 34 are pending. Claim 31 has been amended in accordance with the Examiner's suggestions. No new matter is added. Reconsideration of the objection is therefore requested.

A. Claims 31 and 34 have been rejected under 35 USC §103(a) as unpatentable over Hoekstra et al in view of Meyn et al.

The Examiner alleges that Hoekstra teaches assays for identifying ATM modulators and Meyn teaches that ATM phosphorylates p53, so it would be obvious for the skilled artisan to combine these disclosures to arrive at the claimed invention.

> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

In rejecting the claims, it appears that the Examiner may have misinterpreted the references. It is apparent from a more detailed analysis that the combined teachings of Hoekstra and Meyn do not teach or suggest all the limitations of the claimed invention.

Hoekstra relates to the kinase activity of PIK-related proteins MCSS1 and ATM. Outside the background discussion, there are two references to p53. Page 11 lines 3-10 refers to the use of MCSS1 inhibitors to sensitize p53 deficient cancers to chemotherapy or radiation therapy. There is no suggestion of the possibility of MCSS1 interacting with p53 and no mention of ATM whatsoever. Page 43 lines 12 to 14 describes experimental data showing that neither MCSS1 or ATR phosphorylate p53 at a known phosphorylation site. This is significant, as it would lead one of ordinary skill in the art away from the claimed invention.

Hoekstra is therefore entirely silent about the phosphorylation of p53 by ATM. For the reasons set out below, this deficiency is not remedied by any teaching contained in Meyn.

Contrary to the Examiner's assertion, Meyn does not teach that ATM physically interacts with p53 and does not suggest that ATM can phosphorylate p53.

On page 5997, Meyn states:

'*How far upstream of p53 the ATM protein functions in the signal transduction network is not certain.*'

Thus, although ATM is known to function somewhere upstream of p53 in the signal transduction network (see also figure 1), it is not known how far upstream, *i.e.* ATM and p53 are separated by an unknown number of members of the signal transduction network.

Because p53 is reported to be required for the induction of apoptotic cell death by ionizing radiation in peripheral mouse lymphocytes, Meyn 'suggests' on page 5998 that p53 might mediate cellular decisions to trigger programmed cell death in the face of DNA damage. If this is true, then Meyn sets out two possibilities.

Firstly, Meyn states:

> *'...a normal function of the wild-type ATM polypeptide may be to promote survival in cells that have sustained DNA damage by physically interacting with the p53 protein'*

Secondly, Meyn states:

> *'Alternatively, the ATM protein may counteract p53-mediated apoptosis indirectly, perhaps by inhibiting a step in apoptosis that is downstream of p53.'*

There is no experimental evidence to support either of these possibilities. Meyn therefore provides only a speculative hypothesis that p53 might be involved in the induction of DNA damage induced apoptosis and suggests that, if this hypothesis is true, then p53 might physically interact with ATM in some unspecified way, or it might not.

This is neither experimental evidence nor positive teaching in Meyn that there is any physical interaction between p53 and ATM, and Meyn is entirely silent about the nature of this physical interaction and whether or not it is mediated by other members of the signal transduction network, bearing in mind the statement on page 5997 that it is not certain how far upstream of p53 the ATM protein functions in the signal transduction network.

The Examiner alleges that page 5997 of Meyn suggests that ATM phosphorylates p53. However, there is, in fact, no such suggestion on page 5997 or anywhere else in Meyn. Meyn discusses the activity and function of DNA-PK_{cs} and mentions its ability to phosphorylate a range of proteins *in vivo*, including p53. However, Meyn also states that:

'...ATM and DNA-PK_{cs} act early and independently in separate signal transduction pathways that respond to DNA damage.'

Thus, there is nothing in Meyn which provides any suggestion that ATM acts on the same substrates as DNA-PKcs and phosphorylates p53. In any event, even if such a suggestion were made, it would be refuted by the experimental evidence of Hoekstra, which shows that ATM does not phosphorylate a p53 peptide containing the DNA-PK_{cs} phosphorylation site.

The combination of Heokstra and Meyn is therefore deficient in any teaching that ATM or ATR phosphorylate p53 and does not teach all the limitations of the claimed invention. In the absence of the knowledge that p53 is a substrate for ATM phosphorylation, the skilled person could not combine the disclosures of Heokstra and Meyn to arrive at the present invention.

In view of the above remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 103. Withdrawal of the rejection is therefore requested.

B. Claims 31 and 34 were rejected under 35 USC §103 as unpatentable over Hoekstra in view of Baskaran et al.

The Examiner alleges that Hoekstra teaches assays for identifying ATM modulators and Baskaran suggests that ATM phosphorylates p53, so it would be obvious for the skilled artisan to combine these disclosures to arrive at the claimed invention.

> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

In rejecting the claims, it appears that the Examiner may have misinterpreted the references. It is apparent from a more detailed analysis that the combined teachings of Hoekstra and Baskaran do not teach or suggest all the limitations of the claimed invention.

For the reasons set out above, Hoekstra is entirely silent about the phosphorylation of p53 by ATM. This deficiency is not remedied by any teaching contained in Baskaran.

The Examiner alleges that page 517 of Baskaran suggests that ATM phosphorylates p53. However, there is, in fact, no such suggestion on page 517 or anywhere else in Baskaran.

Page 517 of Baskaran describes the results of the experiments set out in Figure 1, which show that ionizing radiation activated c-Abl kinase in p53 deficient cells but did not activate c-Abl kinase in ATM deficient cells.

Baskaran concludes (page 517 2nd col 1st para) that:

'Thus, c-Abl and p53 are distinct <u>downstream</u> targets of ATM' (emphasis added).

In other words, p53 and c-Abl are independent of each other and operate in different pathways somewhere downstream of ATM. There is no suggestion that these experiments show that ATM acts directly on p53 and c-Abl rather than via intermediate members of these different pathways.

Baskaran goes on to investigate the phosphorylation of c-Abl by the ATM kinase domain (figures 2 and 3), but is entirely silent about any phosphorylation of p53. Given that they are shown to be distinct targets in different pathways, no inferences about the possibility of p53 phosphorylation can be drawn from the phosphorylation of c-Abl and there is nothing in Baskaran which provides any suggestion that p53 is phosphorylated by ATM in the same way as c-Abl.

As Baskaran is silent about the phosphorylation of p53 by ATM, it does not remedy the deficiency of Hoekstra. The combination of Heokstra and Baskaran is therefore deficient in any teaching that ATM or ATR phosphorylate p53 and does not teach all the limitations of the claimed invention. In the absence of any knowledge that p53 is a substrate for ATM phosphorylation, the disclosures of Heokstra and Meyn could not be combined to arrive at the present invention.

In view of the above remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 103. Withdrawal of the rejection is therefore requested.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number MEWE-010.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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By: Pamela Sherwood
Pamela J. Sherwood
Registration No. 36,677

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231